

UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No.: PH-7038
First Named Inventor: Wong, Pancras C.

Express Mail Label No.: EL502308019US

TITLE: Treatment of Thrombosis by Combined Use of a Factor Xa Inhibitor and Aspirin, Tissue Plasminogen Activator (TPA), a GPIIb/IIIb Antagonist, Low Molecular Weight Heparin or Heparin

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

ADDRESS TO: Assistant Commissioner for Patents
Box Patent Application
Washington, DC 20231

1. ☒ Fee (Authority to charge deposit account below.)
(submit on original, and a duplicate for fee processing)
2. ☒ Specification -----[Total Pages (32)]
(preferred arrangement set forth below)
- Descriptive title of the invention
- Cross References to Related Applications (if needed)
- Statement Regarding Fed sponsored R&D (if needed)
- Reference to Microfiche Appendix (if filed)
- Background of the Invention
- Brief Summary of the Invention
- Brief Description of the Drawings (if filed)
- Detailed Description
- Claim(s) -----[No. of Claims 8]
- Abstract of the Disclosure

6. ☐ Microfiche Computer Program (Appendix)
7. Nucleotide and/or Amino Acid Sequences Submission
(if applicable, all necessary)
- a. ☐ Computer Readable Copy
- b. ☐ Paper Copy (identical to computer copy)
- c. ☐ Statement verifying identity of above copies

3. ☒ Drawing(s) (35 USC 113) -----[Total Pages 5]
4. ☒ Oath or Declaration -----[Total Pages 1]
- a. ☒ Unexecuted (original or copy)
- b. ☐ Copy from a prior application (37 CFR 1.63(d))
(for continuation/divisions with Box 14 completed)

☐ DELETION OF INVENTORS

Signed Statement below at 15 deleting
inventor(s) named in the prior application,
see 37 CFR 1.63(d)(2) and 1.33(b).

5. ☐ Incorporation by Reference (useable if Box 4b is
checked) The entire disclosure of the prior application,
which a copy of the oath or declaration is supplied under
Box 4b, is considered as being part of the disclosure of
the accompanying application and is hereby incorporated
by reference therein.

ACCOMPANYING APPLICATION PARTS

8. ☐ Power of Attorney
9. ☐ Information Disclosure Statement (IDS) /Cover
Letter plus PTO-1449
- a. ☐ Copies of IDS Citations ()
10. ☐ Preliminary Amendment (See item 16. below)
11. ☒ Return Receipt Postcard (MPEP 503)
(Should be specifically itemized)
12. ☐ Certified Copy of Priority Document(s)
(if foreign priority is claimed)
13. ☐ Other

14. If a CONTINUATION APPLICATION, check appropriate box and supply the requisite information:

☐ Continuation ☐ Divisional ☐ Continuation-in-part(CIP) of prior application No.: ____/____

DELETION OF INVENTOR(S) STATEMENT

15. ☐ This application is being filed by less than all the inventors named in the prior application. In accordance with
37 CFR 1.63(d)(2) and 1.33(b), the Assistant Commissioner is requested to delete the name(s) of the following person
who are not inventors of the invention being claimed in this application:
16. ☐ Amend the specification, in accordance with MPEP 201.11, by inserting before the first line the sentence:
17. ☐ Priority of foreign application No. _____ filed on _____ in
_____ is claimed under 35 U.S.C. 119.

03/06/00
09519183
030600

35781 U.S. PTO
03/06/00

09519183 * 030600

Attorney Docket No.: PH-7038

First Named Inventor: Wong, Pancras C.

CLAIMS	(1) FOR	(2) NUMBER FILED	(3) NUMBER EXTRA	(4) RATE	(5) CALCULATIONS
	TOTAL CLAIMS (37 CFR 1.16(c))	8 =	0	x \$ 18 =	\$0
	INDEPENDENT CLAIMS (37 CFR 1.16(b))	2 =	0	x \$ 78 =	\$0
	MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ \$ 260 =	\$0
				BASIC FEE (37 CFR 1.16(a))	+ \$690.00
				Total =	\$690.00

18. The Commissioner is hereby authorized to credit overpayments or charge the following fees to Deposit Account No. 04-1928:

a. ☒ Fees required under 37 CFR 1.16


b. ☐ Fees required under 37 CFR 1.17.

19. ☐ Other:

20. CORRESPONDENCE ADDRESS

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21. SIGNATURE OF ATTORNEY OR AGENT REQUIRED

NAME	Kenneth B. Rubin	Reg. No. 36,259
SIGNATURE		
DATE	March 6, 2000	

00519189 030600 005050 08161560

Title

5 Treatment of Thrombosis by Combined Use of a
Factor Xa Inhibitor and Aspirin, Tissue Plasminogen
Activator (TPA), a GPIIb/IIIa Antagonist, Low Molecular
Weight Heparin or Heparin.

10

Field of the Invention

00519138 030600
This invention relates to the treatment of
thrombosis in mammals and more particularly to such
15 treatment by the administration of a combination of (i)
a Factor Xa inhibitor, and (II) a compound selected
from the group consisting of aspirin, TPA, GPIIb/IIIa
antagonist, low molecular weight heparin and heparin,
wherein the dose administered for at least one of (i)
20 and (ii) is a subtherapeutic dose.

Background of the Invention

The selected class of Factor Xa inhibitors and the
25 selected class of aspirin, GPIIb/IIIa antagonist,
tissue plasminogen activator (TPA), low-molecular-
weight-heparin and heparin are essential as component
parts of the novel compositions of this invention.
Aspirin and GPIIb/IIIa antagonists are known in the art
30 as antiplatelet agents. Tissue plasminogen activator
(TPA) is known as a thrombolytic agent. Low-molecular-
weight heparin and heparin are known as anticoagulants.

Factor Xa is a blood coagulation protein. It
plays a major role in blood coagulation because of its
35 central position at the convergent point of the

intrinsic and extrinsic pathways of coagulation. It is believed that inhibition of Factor Xa may eliminate the production of thrombin by either the extrinsic or intrinsic pathways without interfering with a basal level of thrombin activity necessary for normal hemostasis (Harke LA, Hanson SR and Kelly AB. Antithrombotic strategies targeting thrombin activities, thrombin receptors and thrombin generation. Thrombosis and Haemostasis 78: 736-741, 1997).

Both peptide and nonpeptide Factor Xa inhibitors are currently available (Kaiser B. Thrombin and factor Xa inhibitors. Drugs of the Future 23: 423-436, 1998). Examples of peptide Factor Xa inhibitors are antistasin and tick anticoagulant peptide, and nonpeptide Factor Xa inhibitors are described in WO98/2326, Thromb Haemost 1994; 71: 314-9, Thromb Haemost 1994; 72:393-6, and Thromb Haemost 1998; 79: 859-64. The antithrombotic effects of these peptide and nonpeptide Factor Xa inhibitors have been well demonstrated in various experimental models of arterial and venous thrombosis (Kaiser B. Thrombin and factor Xa inhibitors. Drugs of the Future 23: 423-436, 1998).

Summary of the Invention

One object of the present invention is to provide a method of treating thrombosis in a mammal comprising: administering to said mammal a therapeutically effective amount of a combination of (i) a Factor Xa inhibitor, and (ii) a compound selected from the group consisting of aspirin, TPA a GPIIb/IIIa antagonist, low molecular weight heparin and heparin, wherein the dose administered for at least one of (i) and (ii) is a subtherapeutic dose.

Another object of the present invention is to provide a method of treating thrombosis in a mammal wherein the combination of (i) and (ii) above are administered in amounts to provide a synergistic effect.

These and other objects, which will become apparent during the following detailed description, have been achieved by the discovery that the administration of a Factor Xa inhibitor (i) in combination with one of (ii) aspirin, tissue plasminogen activator (TPA), a GPIIb/IIIa antagonist, low molecular weight heparin or heparin, with at least one of (i) and (ii), preferably both, being administered at a dose which would be a subtherapeutic dose when administered alone.

Brief Description of Drawings

Fig. 1 is a graph showing carotid blood flow versus time for saline vehicle, aspirin alone, a Factor Xa inhibitor alone, and a combination of aspirin and the same Factor Xa inhibitor;

Fig. 2 is a graph showing carotid blood flow versus time for saline vehicle, a GPIIb/IIIa antagonist alone, a Factor Xa inhibitor alone, and a combination of the same IIB/IIIa antagonist and Factor X inhibitor;

Fig. 3 is a graph showing carotid blood flow versus time for saline vehicle, fragmin, a Factor Xa inhibitor, and a combination of fragmin and the same Factor Xa inhibitor;

Fig. 4 is a bar chart showing the duration of patency for saline vehicle, a Factor Xa inhibitor alone, TPA alone, and a combination of the same TPA and Factor Xa inhibitor; and

Fig. 5 is a bar chart showing the antithrombotic effect of a saline vehicle and heparin alone, and a combination of heparin with 3 different doses of a Factor Xa inhibitor.

Detailed Description of the Invention

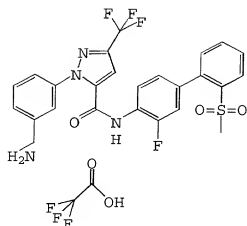
The combinations of active compounds (i) and (ii) of this invention are useful in the treatment of thrombotic disorders including atherosclerotic arterial disease, valvular heart disease, heart failure, cerebrovascular disease such as stroke, atrial fibrillation, coronary artery disease such as myocardial infarction and unstable angina, coronary artery bypass grafts, peripheral vascular disease, thromboembolic complications of prosthetic cardiovascular devices such heart valves and vascular grafts and deep vein thrombosis following major orthopaedic surgery, major fractures and/or abdominal surgery. These combinations are also expected to be useful in combining with endovascular stenting procedures such as percutaneous transluminal coronary angioplasty to prevent subsequent arterial thrombus formation and reocclusion.

Factor Xa inhibitor compounds (i) useful in the present invention are well-known in the prior art. Preferred Factor Xa inhibitors are described in PCT Pat. Appln. No. US97/22895, filed December 15, 1997; published July 2, 1998, as WO98/28269, the disclosure

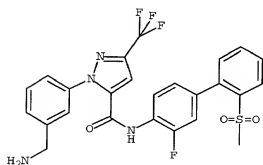
of which is hereby incorporated by reference.
Specifically preferred compounds within W098/28269 are:

0090E0-88161560

Compound (1) :

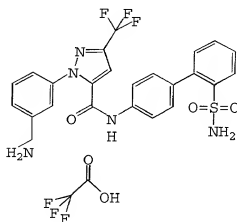


Compound (2) :



HCl Salt

Compound (3) :

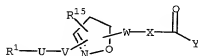


Another Factor Xa inhibitor compound is DX-9065a described in Thromb Haemost 1994; 71:314-9; and Thromb Haemost 1994; 72:393-6. DX-9065a is (+)-2S-2[4-[[[(3S)-1-acetimidoyl-3-pyrrolidinyl]oxy]phenyl]-3-[7-amidino-

2-naphthyl] propanoic acid hydrochloride pentahydrate.
 A still further Factor Xa inhibitor compound is YM-
 60828 described in Thromb Haemost 1998; 79:859-64. YM-
 60828 is [N-[4-[(1-acetimidoyl-4-piperidyl)oxy]
 5 phenyl]-N-[(7-amidino-2-naphthyl)methyl]sulfamoyl]
 acetic acid dihydrochloride. Other Factor Xa inhibitor
 compounds will be readily known by those skilled in the
 art.

10 The compounds (ii) useful in the combination of
 the present invention are either commercially available
 and/or well-known in the prior art. Aspirin, fragmin
 (Pharmacia AB, Stockholm, Sweden), heparin (Upjohn,
 Kalamazoo, Michigan), and TPA (Genentech, San
 15 Francisco, California) are available commercially.
 Fragmin is a low molecular weight heparin. It is
 isolated from standard heparin with a mean molecular
 weight of 4.5 kDa whereas standard heparin has a
 molecular weight of 750 to 1000 kDa. Low-molecular-
 20 weight heparin such as fragmin differs from heparin in
 both their pharmacokinetic properties and mechanism of
 action. The potency for fragmin is expressed in unit
 of anti-Factor Xa activity. Each mg of fragmin has
 about 150 U of anti-Factor Xa activity.

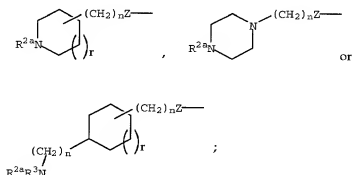
25 Preferred GPIIb/IIIa antagonist compounds useful
 as component (ii) of the combination are described in
 published PCT Application WO95/14683, published 1 June
 1995, as the second embodiment. Preferred compounds
 30 described therein have the formula:



(Ia)

or a pharmaceutically acceptable salt thereof,
 5 wherein:

- R1 is selected from R2a(R3)N-, R2(R3)N(R2N=)C-,
 R2a(R3)N(CH2)p'Z-, R2(R3)N(R2N=)C(CH2)p"Z-,
 R2(R3)N(R2N=)CN(R2)-, R2(R3)NC(O)-, R2(R5O)N(R2N=)C-,
 10 R2(R3)N(R5ON=)C-;



Z is selected from a bond, O, or S;

- 15 R2 and R3 are independently selected from: H; C1-C6 alkyl; C7-C11 arylalkyl optionally substituted with 0-3 groups selected from hydroxy, halogen, C1-C6 alkoxy, C1-C6 alkyl, CF3, S(O)mCH3, -N(CH3)2, C1-C4 haloalkyl,
 20 methylenedioxydiyl, ethylenedioxydiyl; (C1-C10 alkoxy)carbonyl; aryl(C1-C10 alkoxy)carbonyl where the aryl group is optionally substituted with 0-3 groups selected from hydroxy, halogen, C1-C6 alkoxy, C1-C6 alkyl, CF3, S(O)mCH3, -N(CH3)2, C1-C4 haloalkyl,
 25 methylenedioxydiyl, ethylenedioxydiyl; or heteroaryl(C1-C5)alkyl where the heteroaryl group is optionally substituted with 0-2 groups selected from hydroxy, halogen, C1-C6 alkoxy, C1-C6 alkyl, CF3, S(O)mCH3, -N(CH3)2, C1-C4 haloalkyl,

methylenedioxydiyl, ethylenedioxydiyl;

R2a is R2 or R2(R3)N(R2N=)C;

5 U is a single bond,

V is selected from:

a single bond;

10 -(C1-C7 alkyl)-, substituted with 0-3 groups

independently selected from R⁶ or R⁷;

-(C2-C7 alkenyl)-, substituted with 0-3 groups

independently selected from R⁶ or R⁷;

-(C2-C7 alkynyl)-, substituted with 0-3 groups

15 independently selected from R⁶ or R⁷;

-(phenyl)-Q-, said phenyl substituted with 0-2

groups independently selected from R⁶ or R⁷;

-(pyridyl)-Q-, said pyridyl substituted with 0-2

groups independently selected from R⁶ or R⁷;

20 or

-(pyridazinyl)-Q-, said pyridazinyl substituted

with 0-2 groups independently selected from R⁶

or R⁷,

25 Q is selected from

a single bond,

-O-, -S(O)_m-, -N(R¹²)-, -(CH₂)_m-, -C(=O)-, -

N(R^{5a})C(=O)-, -C(=O)N(R^{5a})-, -CH₂O-, -OCH₂-, -

CH₂N(R¹²)-, -N(R¹²)CH₂-, -CH₂C(=O)-, -C(=O)CH₂-, -

30 CH₂S(O)_m-, or -S(O)_mCH₂-,

provided that when b is a single bond, and R¹-U-V-
is a substituent on C5 of the central 5-membered

ring of Formula Ic, then Q is not -O-, -S(O)_m-, -N(R¹²)-, -C(=O)N(R^{5a})-, -CH₂O-, CH₂N(R¹²)- or -CH₂S(O)_m-;

5 W is selected from:
 -(C(R⁴)₂)-C(=O)-N(R^{5a})-, or
 -C(=O)-N(R^{5a})-(C(R⁴)₂)-;

X is -C(R⁴)(R⁸)-CHR^{4a}-;

10

R⁴ is selected from H, C₁-C₁₀ alkyl, C₁-C₁₀ alkylcarbonyl, aryl, arylalkyl, cycloalkyl, or cycloalkylalkyl;

15 R^{4a} is selected from hydroxy, C₁-C₁₀ alkoxy, nitro, -N(R⁵)R^{5a}, -N(R¹²)R¹³, or -N(R¹⁶)R¹⁷, aryl substituted with 0-3 R⁶, or (C₁-C₁₀ alkyl)carbonyl;

20 R^{4b} is selected from H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, hydroxy, C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₁-C₆ alkylsulfinyl, C₁-C₆ alkylsulfonyl, nitro, (C₁-C₆ alkyl)carbonyl, C₆-C₁₀ aryl, -N(R¹²)R¹³, halo, CF₃, CN, (C₁-C₆ alkoxy)carbonyl, carboxy, piperidinyl, morpholinyl or pyridyl;

25

R⁵ is selected from H or C₁-C₁₀ alkyl substituted with 0-6 R^{4b};

30

R^{5a} is selected from hydrogen, hydroxy, C₁ to C₈ alkyl,

C₂ to C₆ alkenyl, C₃ to C₁₁ cycloalkyl, C₄ to C₁₁ cycloalkylmethyl, C₁-C₆ alkoxy, benzyloxy, C₆ to C₁₀ aryl, heteroaryl, heteroarylalkyl, C₇ to C₁₁ arylalkyl, or adamantylmethyl, C₁-C₁₀ alkyl

5 substituted with 0-2 R^{4b};

alternately, R⁵ and R^{5a} can be taken together to be 3-azabicyclononyl, 1,2,3,4-tetrahydro-1-quinolinyl, 1,2,3,4-tetrahydro-2-isoquinolinyl, 1-piperidinyl, 1-morpholinyl, 1-pyrrolidinyl, thiamorpholinyl, thiazolidinyl or 1-piperazinyl, each being optionally substituted with C₁-C₆ alkyl, C₆-C₁₀ aryl, heteroaryl, C₇-C₁₁ arylalkyl, (C₁-C₆ alkyl)carbonyl, (C₃-C₇ cycloalkyl)carbonyl, (C₁-C₆ alkoxy)carbonyl or (C₇-C₁₁ arylalkoxy)carbonyl;

R^{5b} is selected from C₁-C₈ alkyl, C₂-C₆ alkenyl, C₃-C₁₁ cycloalkyl, C₄-C₁₁ cycloalkylmethyl, C₆-C₁₀ aryl, C₇-C₁₁ arylalkyl, or C₁-C₁₀ alkyl substituted with 0-2 R^{4b}

Y is selected from hydroxy, C₁ to C₁₀ alkyloxy, C₃ to C₁₁ cycloalkyloxy, C₆ to C₁₀ aryloxy, C₇ to C₁₁ aralkyloxy, C₃ to C₁₀ alkylcarbonyloxyalkyloxy, C₃ to C₁₀ alkoxycarbonyloxyalkyloxy, C₂ to C₁₀ alkoxycarbonylalkyloxy, C₅ to C₁₀ cycloalkylcarbonyloxyalkyloxy, C₅ to C₁₀ cycloalkoxycarbonyloxyalkyloxy, C₅ to C₁₀ cycloalkoxycarbonylalkyloxy, C₇ to C₁₁ aryloxcarbonylalkyloxy, C₈ to C₁₂ aryloxcarbonyloxyalkyloxy, C₈ to C₁₂ arylcarbonyloxyalkyloxy, C₅ to C₁₀

alkoxyalkylcarbonyloxyalkyloxy, C₅ to C₁₀ (5-alkyl-1,3-dioxo-cyclopenten-2-one-yl)methyloxy, or C₁₀ to C₁₄ (5-aryl-1,3-dioxo-cyclopenten-2-one-yl)methyloxy;

5

R⁶ and R⁷ are each independently selected from H, C₁-C₁₀ alkyl, hydroxy, C₁-C₁₀ alkoxy, nitro, (C₁-C₁₀ alkyl)carbonyl, -N(R¹²)R¹³, cyano, or halo;

10 R¹² and R¹³ are each independently selected from H, C₁-C₁₀ alkyl, (C₁-C₁₀ alkoxy)carbonyl, (C₁-C₁₀ alkyl)carbonyl, C₁-C₁₀ alkylsulfonyl, aryl(C₁-C₁₀ alkyl)sulfonyl, arylsulfonyl, heteroarylsulfonyl, heteroarylcarbonyl,
 15 heteroarylalkylcarbonyl or aryl, wherein said aryl groups being optionally substituted with 0-3 substituents selected from the group consisting of: C₁-C₄ alkyl, C₁-C₄ alkoxy, halo, CF₃, and NO₂;

20 R¹⁵ is selected from H, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₁₀ alkoxy, aryl, heteroaryl or (C₁-C₁₀ alkoxy)carbonyl, CO₂R⁵ or -C(=O)N(R⁵)R^{5a};

R¹⁶ is selected from:

25 -C(=O)-O-R^{18a},
 -C(=O)-R^{18b},
 -C(=O)N(R^{18b})₂,
 -SO₂-R^{18a}, or
 -SO₂-N(R^{18b})₂;

30

R¹⁷ is selected from: H or C₁-C₅ alkyl ;

R^{18a} is selected from:

- C₁-C₈ alkyl substituted with 0-2 R¹⁹,
 C₂-C₈ alkenyl substituted with 0-2 R¹⁹,
 C₂-C₈ alkynyl substituted with 0-2 R¹⁹,
 5 C₃-C₈ cycloalkyl substituted with 0-2 R¹⁹,
 aryl substituted with 0-4 R¹⁹,
 aryl(C₁-C₆ alkyl)- substituted with 0-4 R¹⁹,

 a heterocyclic ring system selected from
 10 pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl,
 pyrazolyl, triazolyl, imidazolyl, benzofuranyl,
 indolyl, indolinyl, quinolinyl, isoquinolinyl,
 isoxazolyl, isoxazoliny, benzimidazolyl,
 piperidinyl, tetrahydrofuranyl, pyranyl,
 15 pyrimidinyl, 3*H*-indolyl, pyrrolidinyl,
 piperidinyl, indolinyl, or morpholinyl, said
 heterocyclic ring being substituted with 0-4 R¹⁹;

 C₁-C₆ alkyl substituted with a heterocyclic ring
 20 system selected from pyridinyl, furanyl,
 thiazolyl, thienyl, pyrrolyl, pyrazolyl,
 imidazolyl, isoxazolyl, isoxazoliny, benzofuranyl,
 indolyl, indolenyl, quinolinyl,
 isoquinolinyl, benzimidazolyl, piperidinyl,
 25 tetrahydrofuranyl, pyranyl, pyridinyl, 3*H*-indolyl,
 indolyl, pyrrolidinyl, piperidinyl, indolinyl, or
 morpholinyl, said heterocyclic ring being
 substituted with 0-4 R¹⁹;

 30 R^{18b} is selected from R^{18a} or H;

 R¹⁹ is selected from H, halogen, CF₃, CN, NO₂, NR¹²R¹³,
 C₁-C₈ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆

alkoxy, C₃-C₁₁ cycloalkyl, C₄-C₁₁ cycloalkylalkyl, aryl, heteroaryl, aryl(C₁-C₆ alkyl)-, (C₁-C₄ alkyl)sulfonyl, aryl-sulfonyl, or C₁-C₄ alkoxycarbonyl;

5

n is 0-4;

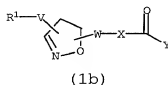
p' is 1-7;

p'' is 1-7;

r is 0-3.

10

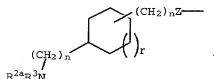
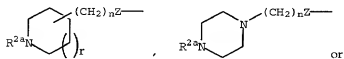
More preferred compounds have the formula:



15

or a pharmaceutically acceptable salt thereof, wherein:

R¹ is selected from: R^{2a}(R³)N-, R²NH(R²N=)C-,
 20 R²NH(R²N=)CNH-, R^{2a}(R³)N(CH₂)_{p'}Z-,
 R²NH(R²N=)C(CH₂)_{p''}Z-, R²(R³)NC(O)-,
 R²(R⁵O)N(R²N=)C-, R²(R³)N(R⁵ON=)C-;



25

n is 0-1;

p' is 4-6;

5 p" is 2-4;

Z is selected from a bond or O;

V is a single bond, -(phenyl)- or -(pyridyl)-;

10

W is selected from:

-C(R⁴)₂-C(=O)-N(R^{5a})-,

-C(=O)-N(R^{5a})-CH₂-;

15 X is selected from:

-CH₂-CH(N(R¹⁶)R¹⁷)-, or

-CH₂-CH(NR⁵R^{5a})-;

Y is selected from:

20

hydroxy;

C₁ to C₁₀ alkoxy;

methylcarbonyloxymethoxy-;

ethylcarbonyloxymethoxy-;

t-butylcarbonyloxymethoxy-;

25

cyclohexylcarbonyloxymethoxy-;

1-(methylcarbonyloxy)ethoxy-;

1-(ethylcarbonyloxy)ethoxy-;

1-(*t*-butylcarbonyloxy)ethoxy-;

1-(cyclohexylcarbonyloxy)ethoxy-;

30

i-propyloxycarbonyloxymethoxy-;

t-butyloxycarbonyloxymethoxy-;

1-(*i*-propyloxycarbonyloxy)ethoxy-;

1-(cyclohexyloxycarbonyloxy)ethoxy-;

1-(*t*-butyloxycarbonyloxy)ethoxy-;

dimethylaminoethoxy-;
 diethylaminoethoxy-;
 (5-methyl-1,3-dioxacyclopenten-2-on-4-yl)methoxy-;
 (5-(*t*-butyl)-1,3-dioxacyclopenten-2-on-4-
 5 yl)methoxy-;
 (1,3-dioxa-5-phenyl-cyclopenten-2-on-4-
 yl)methoxy-;
 1-(2-(2-methoxypropyl)carbonyloxy)ethoxy-;

10 R¹⁶ is selected from:

-C(=O)-O-R^{18a},
 -C(=O)-R^{18b},
 -S(=O)₂-R^{18a} or
 -SO₂-N(R^{18b})₂;

15

R¹⁷ is selected from H or C₁-C₅ alkyl;

R^{18a} is selected from:

C₁-C₈ alkyl substituted with 0-2 R¹⁹,
 20 C₂-C₈ alkenyl substituted with 0-2 R¹⁹,
 C₂-C₈ alkynyl substituted with 0-2 R¹⁹,
 C₃-C₈ cycloalkyl substituted with 0-2 R¹⁹,
 aryl substituted with 0-4 R¹⁹,
 aryl(C₁-C₆ alkyl)- substituted with 0-4 R¹⁹,

25

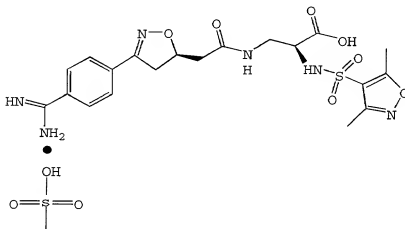
a heterocyclic ring system selected from
 pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl,
 pyrazolyl, triazolyl, imidazolyl, benzofuranyl,
 indolyl, indolinyl, quinolinyl, isoquinolinyl,
 30 isoxazolyl, isoxazolinyl, benzimidazolyl,
 piperidinyl, tetrahydrofuranyl, pyranlyl,
 pyrimidinyl, 3*H*-indolyl, pyrrolidinyl,

piperidinyl, indolinyl, or morpholinyl, said heterocyclic ring being substituted with 0-4 R¹⁹;

C₁-C₆ alkyl substituted with a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, isoxazolyl, isoxazoliny, benzofuranyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranyl, pyridinyl, 3*H*-indolyl, indolyl, pyrrolidinyl, piperidinyl, indolinyl, or morpholinyl, said heterocyclic ring being substituted with 0-4 R¹⁹.

A specifically preferred compound has the formula:

Compound (4):



Other salts of this compound are also specifically preferred.

Specific examples of other GPIIb/IIIa antagonist compounds are abciximab, eptifibatide, tirofiban, lamifiban, lefradafiban, sibrafiban (Ro-48-3657), orbofiban and xemilofiban described in the paper of

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Graul et al. and Scarborough (Graul A, Martel AM and Castaner J. Xemilifiban; Drugs of the Future 22: 508-517, 1997; Scarborough RM; Eptifibatide. Drugs of the Future 23: 585-590, 1998). Others will be readily
5 apparent to those skilled in the art.

"Therapeutically effective amount" is intended to include an amount of a combination of compounds claimed effective to treat thrombosis in a mammal. The
10 combination of compounds is preferably a synergistic combination. Synergy, as described for example by Chou and Talalay, Adv. Enzyme Regul. 22:27-55 (1984), occurs when the effect (in this case, an antithrombotic effect) of the compounds when administered in
15 combination is greater than the additive effect of the compounds when administered alone as a single agent. In general, a synergistic effect is most clearly demonstrated at suboptimal concentrations of the compounds. Synergy can be in terms of antihypertensive
20 effect, antithrombotic effect, or some other non-additive beneficial effect of the combination compared with the individual components.

By "administered in combination", "combination",
25 or "combined" when referring to component (i) and component (ii) of the present invention, it is meant that the components are administered concurrently to the mammal being treated. When administered in combination each component may be administered at the
30 same time or sequentially in any order or at different points in time. Thus, component (i) and component (ii) may be administered separately but sufficiently closely in time so as to provide the desired therapeutic effect.

35

By "subtherapeutic dose" when referring to component (i) and component (ii) of the present invention, it is meant that each component when administered to a mammal alone does not give the desired therapeutic effect for the disease being treated.

The invention can be understood further by the following examples wherein Compounds (1) - (4) are as shown above. Saline (0.9 weight % NaCl) is the vehicle in all examples.

Example 1

The combination of aspirin and a Factor Xa inhibitor

Rabbits were anesthetized with ketamine (50 mg/kg i.m.) and xylazine (10 mg/kg i.m.) and then surgically prepared with arterial and venous catheters. An electromagnetic flow probe was placed on a segment of an isolated carotid artery to monitor blood flow. Thrombus formation was induced by electrical stimulation of the carotid artery for 3 min at 4 mA using an external stainless-steel bipolar electrode. Carotid blood flow was measured continuously over a 90-min period to monitor thrombus occlusion. Test agents were infused intravenously 1 hour prior to the electrical stimulation of the carotid artery and continuously during the 90-min period.

30

As shown in Fig. 1 following the electrical stimulation, thrombus formation was induced and carotid blood flow was gradually declined in saline vehicle-treated animals. At about 40 min after stimulation, the artery was totally occluded and blood flow was

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zero. Aspirin at 1 mg/kg/hr i.v. (concentration in saline was 0.167 mg/ml) or Compound (1) (a Factor Xa inhibitor) at 0.1 mg/kg/hr i.v. (concentration in saline was 0.017 mg/ml) did not prevent the occlusion of the artery; and blood flow in these animals was decreased to zero at about the same time as those in vehicle-treated animals. Surprisingly, Compound (1) 0.1 mg/kg/hr i.v. in combination with aspirin at 1 mg/kg/hr i.v. prevented the artery from occlusion and maintained the blood flow for at least 90 min. These results indicate that a combination of Compound (1) and aspirin at their subtherapeutic doses unexpectedly produced a significant antithrombotic effect in a rabbit model of arterial thrombosis.

Example 2

The combination of Compound (4) (a GP-IIb/IIIa antagonist) and a Factor Xa inhibitor

Experimental protocol was described as above for Example 1. As shown in Figure 2, Compound (4) (a GP-IIb/IIIa antagonist) at 0.03 mg/kg/hr i.v. and Compound (3) (a Factor Xa inhibitor) at 0.1 mg/kg/hr i.v. did not prevent the occlusion of the artery; and blood flow in these animals was decreased to zero at about the same time as those in vehicle-treated animals. Surprisingly, Compound (3) at 0.1 mg/kg/hr i.v. (concentration in saline was 0.017 mg/ml) in combination with Compound (4) at 0.03 mg/kg/hr i.v. (concentration in saline was 0.005 mg/ml) prevented the artery from occlusion and maintained the blood flow for at least 90 min. These results indicate that a combination of Compound (3) and Compound (4) at their subtherapeutic doses unexpectedly produced a

significant antithrombotic effect in a rabbit model of arterial thrombosis.

Example 3

5

The combination of fragmin (low-molecular-weight-heparin) and a Factor Xa inhibitor

Experimental protocol was described as above for
10 Example 1. As shown in Figure 3, fragmin (a low-molecular-weight-heparin) at 60 U/kg/hr i.v. was moderately active. Compound (3) (a Factor Xa inhibitor) at 0.1 mg/kg/hr i.v. did not prevent the occlusion of the artery; and blood flow in these
15 animals was decreased to zero similar to those in vehicle-treated animals. Surprisingly, Compound (3) at 0.1 mg/kg/hr i.v. (concentration in saline was 0.017 mg/ml) in combination with fragmin at 60 U/kg/hr i.v. (concentration in saline was 0.067 mg/ml or 10 U/ml)
20 prevented the artery from occlusion and maintained the blood flow for at least 90 min. These results indicate that a combination of Compound (3) at its subtherapeutic dose and fragmin at a medium dose unexpectedly produced a significant antithrombotic
25 effect in a rabbit model of arterial thrombosis.

Example 4

The combination of recombinant tissue-type plasminogen
30 activator (TPA) and a Factor Xa inhibitor

Experiments were conducted in rats. It is similar to that of the rabbit protocol as described above in Example 1 except that Compound (2) and/or TPA were
35 given 5 min after a preformed clot was formed. The

measured parameter is its duration of patency. As shown in Figure 4, five minutes after the induction of occlusive thrombosis, neither Compound (2) at 5.6 mg/kg (concentration in saline was 0.23 mg/ml) and 1.4 mg/kg/hr i.v. nor TPA at 1 mg/kg i.v. (concentration in saline was 1 mg/ml) produced a therapeutic effect on the duration of patency. However, a combination of Compound (2) at 5.6 mg/kg and 1.4 mg/kg/hr i.v., and TPA at 1 mg/kg i.v. increased the duration of patency to 70%. This result suggests that a Factor Xa inhibitor such as Compound (2) is a promising useful adjunctive agent, which accelerates thrombolysis induced by TPA or other thrombolytic agents. Compound (2) enhanced the thrombolysis induced by a subtherapeutic dose of TPA.

Example 5

The combination of heparin and a Factor Xa inhibitor

Experiments were conducted in male guinea pigs anesthetized with a mixture of ketamine (90 mg/kg i.m.) and xylazine (12 mg/kg i.m.). The arterio-venous shunt was connected between the carotid artery and jugular vein. The exposure of flowing blood to a silk thread induced the formation of a significant thrombus. Thirty minutes later, the shunt was disconnected and the silk thread covered with thrombus was weighed. The compounds or saline vehicle were given as continuous i.v. infusion starting 1 hr before blood was circulated in the shunt and continuing throughout the experiment (i.e., 90 min). As shown in figure 5, heparin at 4 U/kg/hr i.v. (concentration in saline was 0.667 U/ml) did not cause antithrombotic effect. However, heparin at 4 U/kg/hr i.v. potentiated the antithrombotic

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effects of Compound (3) (a Factor Xa inhibitor) at 0.3,
1 or 3 mg/kg/hr i.v. (concentration in saline for 0.3
dose was 0.05 mg/ml). This result suggests that
heparin at a subtherapeutic dose enhances the
5 antithrombotic effect of Compound (3) in a guinea model
of venous thrombosis.

The results presented indicate that a
combination therapy comprising a Factor Xa inhibitor
10 and one of aspirin, TPA, a GPIIb/IIIa antagonist, low
molecular weight heparin or heparin will be effective
in treating thrombosis in patients. The method of the
present invention provides important advantages over
currently available treatments for thrombosis.

15

DOSAGE AND FORMULATION

The Factor Xa inhibitor (i) and a compound (ii) of
this invention can be administered as treatment for
20 thrombosis by any means that produces contact of the
active agent with the agents site of action, i.e.,
Factor Xa, in the body of a mammal. They can be
administered by any conventional means available for
use in conjunction with pharmaceuticals, either as
25 individual therapeutic agents or in a combination of
therapeutic agents. They can be administered alone,
but preferably are administered with a pharmaceutical
carrier selected on the basis of the chosen route of
administration and standard pharmaceutical practice.

30

The dosage administered will, of course, vary
depending upon known factors, such as the
pharmacodynamic characteristics of the particular agent
and its mode and route of administration; the age,
35 health and weight of the recipient; the nature and

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extent of the symptoms; the kind of concurrent
treatment; the frequency of treatment; and the effect
desired. A daily dosage of active ingredient can be
expected to be about 0.001 to about 1000 milligrams per
5 kilogram of body weight, with the preferred dose being
about 0.01 to about 30 mg/kg.

Dosage forms of compositions suitable for
administration contain from about 1 mg to about 100 mg
10 of active ingredient per unit. In these pharmaceutical
compositions the active ingredient will ordinarily be
present in an amount of about 0.5-95% by weight based
on the total weight of the composition. The active
ingredient can be administered orally in solid dosage
15 forms, such as capsules, tablets and powders, or in
liquid dosage forms, such as elixirs, syrups and
suspensions. It can also be administered parenterally,
in sterile liquid dosage forms.

20 Gelatin capsules contain the active ingredient and
powdered carriers, such as lactose, starch, cellulose
derivatives, magnesium stearate, stearic acid, and the
like. Similar diluents can be used to make compressed
tablets. Both tablets and capsules can be manufactured
25 as sustained release products to provide for continuous
release of medication over a period of hours.
Compressed tablets can be sugar coated or film coated
to mask any unpleasant taste and protect the tablet
from the atmosphere, or enteric coated for selective
30 disintegration in the gastrointestinal tract. Liquid
dosage forms for oral administration can contain
coloring and flavoring to increase patient acceptance.

In general, water, a suitable oil, saline, aqueous
35 dextrose (glucose), and related sugar solutions and

glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, 5 suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts, and sodium 10 EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben and chlorobutanol. Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing 15 Company, Easton, PA, 1985, a standard reference text in this field, the disclosure of which is hereby incorporated by reference.

Useful pharmaceutical dosage-forms for 20 administration of the compounds of this invention can be illustrated as follows:

Capsules

A large number of unit capsules can be prepared by 25 filling standard two-piece hard gelatin capsules each with 0.1 to 100 mg of powdered active ingredient, 150 mg of lactose, 50 mg of cellulose, and 6 mg magnesium stearic.

30 Soft Gelatin Capsules

A mixture of active ingredient in a digestible oil such as soybean oil, cottonseed oil or olive oil can be prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin 35 capsules containing 0.1 to 100 mg of the active

ingredient. The capsules should then be washed and dried.

Tablets

- 5 A large number of tablets can be prepared by conventional procedures so that the dosage unit is 0.1 to 100 mg of active ingredient, 0.2 mg of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 mg of microcrystalline cellulose, 11 mg of starch
10 and 98.8 mg of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

Suspension

- An aqueous suspension can be prepared for oral
15 administration so that each 5 mL contain 0.1 to 100 mg of finely divided active ingredient, 200 mg of sodium carboxymethyl cellulose, 5 mg of sodium benzoate, 1.0 g of sorbitol solution, U.S.P., and 0.025 mg of vanillin.

Injectable

- A parenteral composition suitable for
administration by injection can be prepared by stirring
0.1 to 100 mg by weight of active ingredient in 10% by
volume propylene glycol and water. The solution is
25 sterilized by commonly used techniques.

Combination of components (i) and (ii)

- Each therapeutic agent component of this invention can independently be in any dosage form, such as those
30 described above, and can also be administered in various ways, as described above. In the following description component (ii) is to be understood to represent one or more agents as described previously. Thus, if components (i) and (ii) are to be treated the
35 same or independently, each agent of component (ii) may

also be treated the same or independently.

Components (i) and (ii) of the present invention may be formulated together, in a single dosage unit (that is, combined together in one capsule, tablet, powder, or liquid, etc.) as a combination product. When component (i) and (ii) are not formulated together in a single dosage unit, the component (i) may be administered at the same time as component (ii) or in any order; for example component (i) of this invention may be administered first, followed by administration of component (ii), or they may be administered in the reverse order. If component (ii) contains more than one agent, e.g., aspirin and heparin, these agents may be administered together or in any order. When not administered at the same time, preferably the administration of component (i) and (ii) occurs less than about one hour apart. Preferably, the route of administration of component (i) and (ii) is intravenously (i.v.). The terms oral agent, oral inhibitor, oral compound, or the like, as used herein, denote compounds which may be orally administered. Although it is preferable that component (i) and component (ii) both be administered by the same route (that is, for example, both orally) or dosage form, if desired, they may each be administered by different routes (that is, for example, one component of the combination product may be administered orally, and another component may be administered intravenously) or dosage forms.

As is appreciated by a medical practitioner skilled in the art, the dosage of the combination therapy of the invention may vary depending upon various factors such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration, the age, health and weight

of the recipient, the nature and extent of the symptoms, the kind of concurrent treatment, the frequency of treatment, and the effect desired, as described above.

- 5 The proper dosage of components (i) and (ii) of the present invention will be readily ascertainable by a medical practitioner skilled in the art, based upon the present disclosure. By way of general guidance, typically a daily dosage may be about 0.01 milligram to
10 about 1 gram of each component. If component (ii) represents more than one compound, then typically a daily dosage may be about 0.01 milligram to about 0.1 gram of each agent of component (ii). By way of general guidance, when the compounds of component (i)
15 and component (ii) are administered in combination, the dosage amount of each component may be reduced by about 70-80% relative to the usual dosage of the component when it is administered alone as a single agent for the treatment of thrombosis, in view of the synergistic
20 effect of the combination.

- The combination products of this invention may be formulated such that, although the active ingredients are combined in a single dosage unit, the physical contact between the active ingredients is minimized.
25 In order to minimize contact, for example, where the product is orally administered, one active ingredient may be enteric coated. By enteric coating one of the active ingredients, it is possible not only to minimize the contact between the combined active ingredients,
30 but also, it is possible to control the release of one of these components in the gastrointestinal tract such that one of these components is not released in the stomach but rather is released in the intestines.
Another embodiment of this invention where oral
35 administration is desired provides for a combination

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product wherein one of the active ingredients is coated with a sustained-release material which effects a sustained-release throughout the gastrointestinal tract and also serves to minimize physical contact between the combined active ingredients. Furthermore, the sustained-released component can be additionally enteric coated such that the release of this component occurs only in the intestine. Still another approach would involve the formulation of a combination product in which the one component is coated with a sustained and/or enteric release polymer, and the other component is also coated with a polymer such as a low viscosity grade of hydroxypropyl methylcellulose or other appropriate materials as known in the art, in order to further separate the active components. The polymer coating serves to form an additional barrier to interaction with the other component. In each formulation wherein contact is prevented between components (i) and (ii) via a coating or some other material, contact may also be prevented between the individual agents of component (ii).

Dosage forms of the combination products of the present invention wherein one active ingredient is enteric coated can be in the form of tablets such that the enteric coated component and the other active ingredient are blended together and then compressed into a tablet or such that the enteric coated component is compressed into one tablet layer and the other active ingredient is compressed into an additional layer. Optionally, in order to further separate the two layers, one or more placebo layers may be present such that the placebo layer is between the layers of active ingredients. In addition, dosage forms of the present invention can be in the form of capsules wherein one active ingredient is compressed into a

tablet or in the form of a plurality of microtablets, particles, granules or non-perils, which are then enteric coated. These enteric coated microtablets, particles, granules or non-perils are then placed into
5 a capsule or compressed into a capsule along with a granulation of the other active ingredient.

These as well as other ways of minimizing contact between the components of combination products of the present invention, whether administered in a single
10 dosage form or administered in separate forms but at the same time or concurrently by the same manner, will be readily apparent to those skilled in the art, based on the present disclosure.

Obviously, numerous modifications and variations
15 of the present invention are possible in light of the above teachings. It is therefore to be understood that within the scope of the appended claims, the invention may be practiced otherwise than as specifically described herein.

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What is claimed is:

1. A method of treating thrombosis in a mammal comprising: administering to said mammal a
5 therapeutically effective amount of a combination of
(i) a Factor Xa inhibitor, and (ii) a compound selected from the group consisting of aspirin, TPA, a GPIIb/IIIa antagonist, low molecular weight heparin and heparin, wherein the dose administered for at least one of (i)
10 and (ii) is a subtherapeutic dose.
2. A method of Claim 1 wherein the combination of (i) and (ii) provides a synergistic effect.
- 15 3. A method of Claim 2 wherein (ii) is aspirin.
4. A method of Claim 2 wherein (ii) is TPA.
5. A method of Claim 2 wherein (ii) is a GPIIb/IIIa
20 antagonist.
6. A method of Claim 2 wherein (ii) is a low molecular weight heparin.
- 25 7. A method of Claim 2 wherein (ii) is heparin.
8. The use of a combination of (i) a Factor Xa inhibitor, and (ii) a compound selected from the group consisting of aspirin, TPA, a GPIIb/IIIa antagonist,
30 low molecular weight heparin and heparin for the manufacture of a medicament for the treatment of thrombosis.

Title

5 Treatment of Thrombosis by Combined Use of a
Factor Xa Inhibitor and Aspirin, Tissue Plasminogen
Activator (TPA), a GPIIb/IIIa Antagonist, Low Molecular
Weight Heparin or Heparin

Abstract of the Disclosure

10 Provided is a method of treating thrombosis in
mammals by administering therapeutically effective
amounts of a combination of (i) a Factor Xa inhibitor,
15 and (ii) a compound selected from the group consisting
of aspirin, TPA, a GPIIb/IIIa antagonist, low molecular
weight heparin and heparin, wherein the dose
administered for at least one of (i) and (ii) is a
subtherapeutic dose. Preferably, the combination of
20 (i) and (ii) provides a synergistic effect.

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Fig. 1

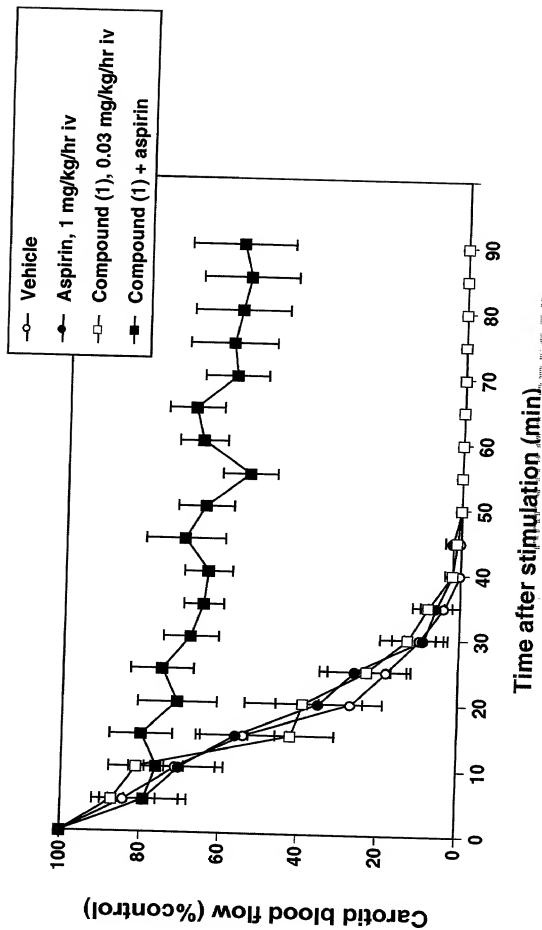


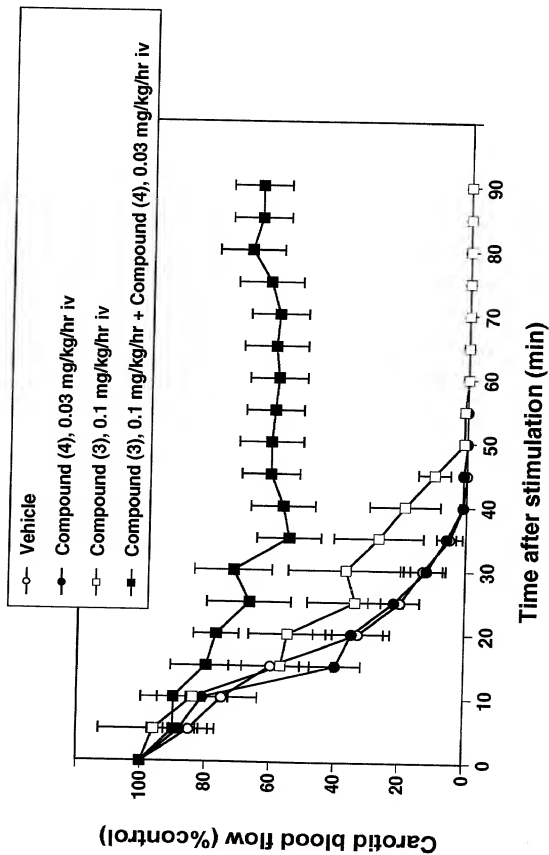
Fig. 2

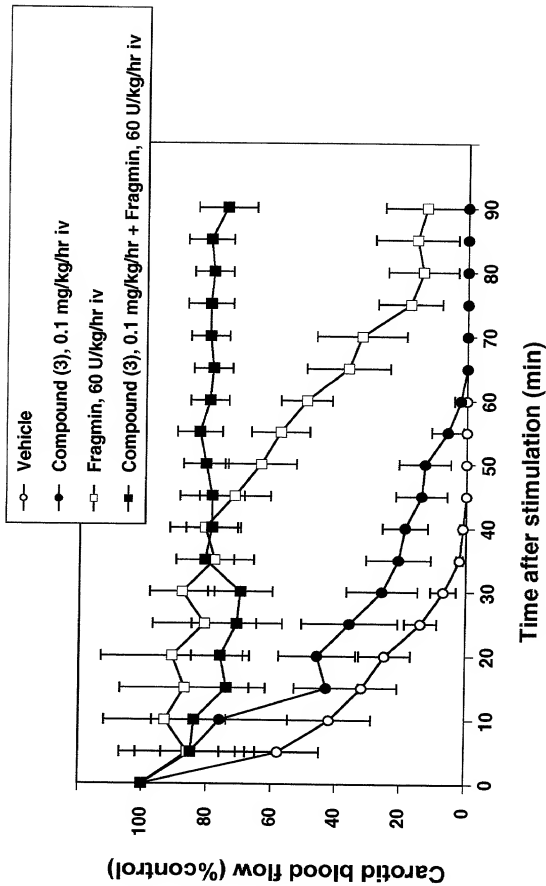
Fig. 3

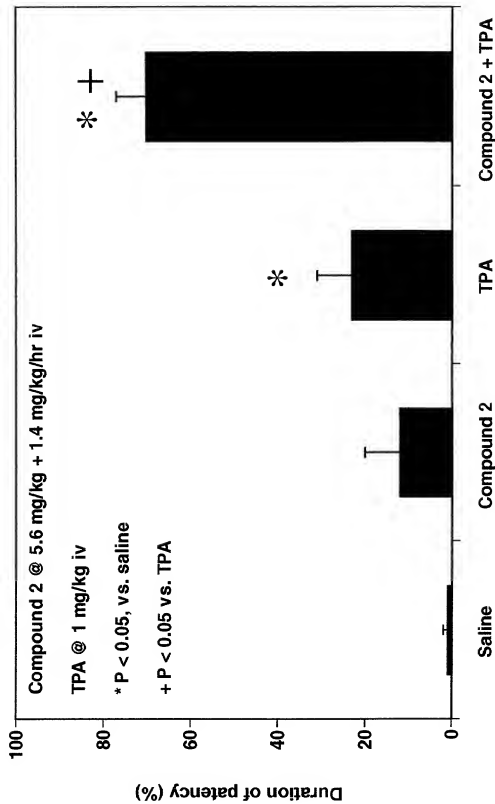
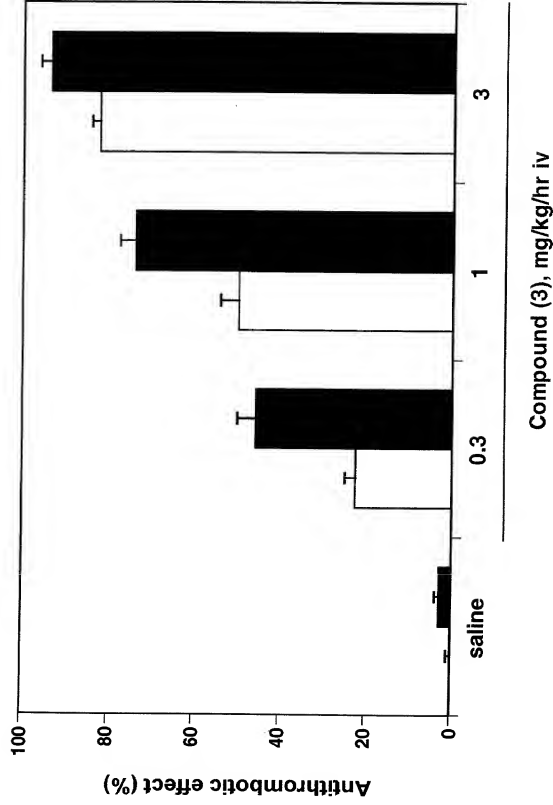
Fig. 4

Fig. 5

DECLARATION and POWER OF ATTORNEY

As a below-named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

Treatment of Thrombosis by Combined Use of a Factor Xa Inhibitor and Aspirin, Tissue Plasminogen Activator (TPA), a GPIIb/IIIa Antagonists, Low Molecular Weight Heparin or Heparin

the specification of which is attached hereto unless the following box is checked:

☐ was filed on _____ as U.S. Application No. _____ or PCT International Application No. _____ and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is known to me to be material to patentability as defined in 37 CFR § 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed.

Application No.	Country	Filing Date	Priority Claimed (Yes/No)
I hereby claim the benefit under 35 U.S.C. § 119(e) of any United States Provisional Application(s) listed below.			
U.S. Provisional Application No.		U.S. Filing Date	
60/123,815		March 11, 1999	

I hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s), or § 365(c) of any PCT International Application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application or PCT International Application in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose information which is known to me to be material to patentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

Application No.	U.S. Filing Date	Status (patented, pending or abandoned)

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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☐ Additional Inventors are being named on separately numbered sheets attached hereto.